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(54) Title: MULTIMERS OF RECEPTOR-BINDING LIGANDS

(57) Abstract: The invention relates to the provision of oligomeric polypeptides (dimers, trimers, etc) comprising the ligand binding domains of cytokines which are linked via flexible polypeptide linker molecules. The linker molecules optionally comprise protease sensitive sites to modulate the release of biologically active cytokines when administered to a human or animal subject.

INTERNATIONAL SEARCH REPORT

In National Application No
PCT 03/00253A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/52 C12N15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WEICH N S ET AL: "INTERLEUKIN-3/ERYTHROPOIETIN FUSION PROTEINS: IN VITRO EFFECTS ON HEMATOPOIETIC CELLS" EXPERIMENTAL HEMATOLOGY, NEW YORK, NY, US, vol. 21, no. 5, May 1993 (1993-05), pages 647-655, XP000983864 ISSN: 0301-472X page 650, left-hand column	1, 2, 9-19, 21-23, 26-29, 39-42
	---	1, 2, 5, 8, 9, 11-15, 18-24, 29, 32-42

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LIESCHKE G ET AL: "Bioactive murine and human interleukin-12 fusion proteins which retain antitumor activity in vivo" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 15, no. 1, January 1997 (1997-01), pages 35-40, XP002106574 ISSN: 1087-0156 the whole document ---	1,2,5,8, 9,11-15, 18-24, 29,32-42
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Int'l Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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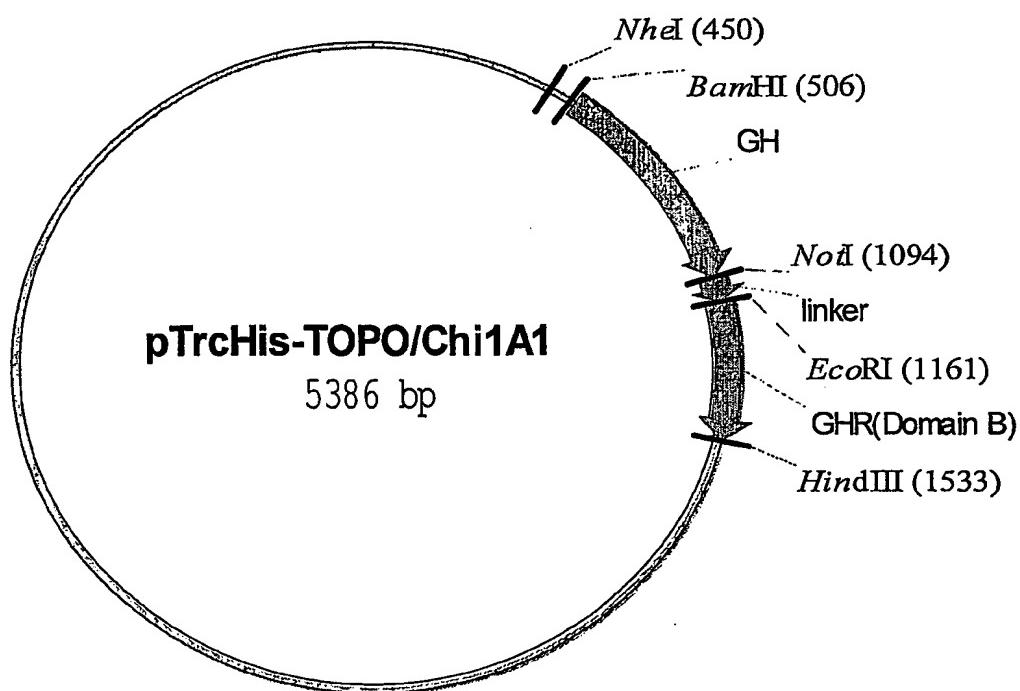
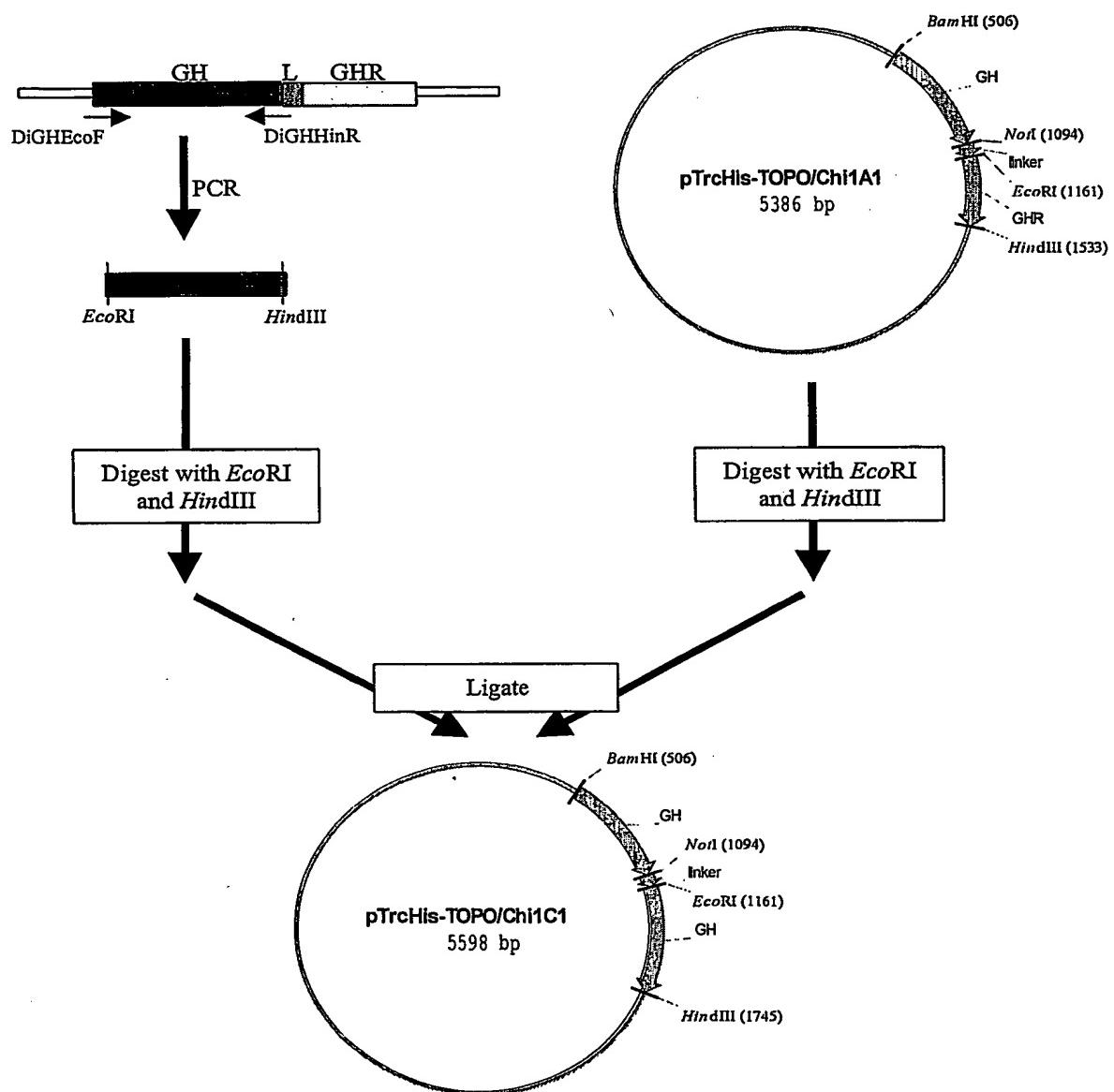


FIGURE 1

Name	5'-Sequence-3'
DiGHEcoF	AGGCGAATTCTTCCCAACCATTCCCTAT (SEQ ID:7)
DiGHNotF	CTTCAAGAGGC GGCGGCCGCTTCCCAACCATTCCCTTAT (SEQ ID:8)
DiGHHinR	TTCCAAGCTTCATCAGAACGCCACAGCTGCCCTCCA (SEQ ID:9)
Lep2TrcFOR	CAAAGCTAGCGGTGGCATGCAAGT (SEQ ID:10)
Lep2TrcREV	AAGCTTGAATT CCTATTACGTCGACTCTAG (SEQ ID:11)
LepLinkFOR	CAGCTGCTGTGGCTTCGGCGGCCGCAGGTGGCGGA (SEQ ID:12)
LepLinkREV	AATGCCCTCGAGGAATT CGGAACCTCCG (SEQ ID:13)
Lep2FOR	GGGAAACTCGAGGTGCCCATCCAAAAAGTCCAAGAT (SEQ ID:14)
Lep2REV	GGGAAAGTCGACTCTAGAGCACCCAGGGCTGAGGTCC (SEQ ID:15)

FIGURE 2

**FIGURE 3**

Growth Hormone Molecule 1

TTCCAACCATTCCCTTATCCAGGTTTGACAACGCTAGTCTCCGCGC
 CCATCGTCTGCACCAGCTGGCCTTGACACCTACCAGGAGTTGAAGAAG
 CCTATATCCAAAGGAACAGAACAGAAGTATTCAATTCCCTGCAGAACCCCCAGACC
 TCCCTCTGTTCTCAGAGTCTATTCCGACACCCCTCAACAGGGAGGAAAC
 ACAACAGAAATCCAACCTAGAGCTGCCGCATCTCCCTGCTGCTCATCC
 AGTCGTGGCTGGAGCCGTGCAGTCCTCAGGAGTGTCTCGCCAACAGC
 CTGGTGTACGGCGCCTCTGACAGCAACGTCTATGACCTCCTAAAGGACCT
 AGAGGAAGGCATCCAAACGCTGATGGGGAGGCTGGAAGATGGCAGCCCCC
 GGACTGGCAGATCTCAAGCAGACCTACAGCAAGTTCGACACAAACTCA
 CACAACGATGACGCACTACTCAAGAACTACGGGCTGCTACTGCTTCAG
 GAAGGACATGGACAAGGTCGAGACATTCCCTGCGCATCGTGCAGTGCCGCT
 CTGTGGAGGGCAGCTGTGGCTTC (SEQ ID:16)

Linker Region

TTAGTGGCGCGCGGCAGTCCGGCATTGGCGGCGGTGGCGGC (SEQ ID:17)

Growth Hormone Molecule 1

TTCCAACCATTCCCTTATCCAGGTTTGACAACGCTAGTCTCCGCGC
 CCATCGTCTGCACCAGCTGGCCTTGACACCTACCAGGAGTTGAAGAAG
 CCTATATCCAAAGGAACAGAACAGAAGTATTCAATTCCCTGCAGAACCCCCAGACC
 TCCCTCTGTTCTCAGAGTCTATTCCGACACCCCTCAACAGGGAGGAAAC
 ACAACAGAAATCCAACCTAGAGCTGCCGCATCTCCCTGCTGCTCATCC
 AGTCGTGGCTGGAGCCGTGCAGTCCTCAGGAGTGTCTCGCCAACAGC
 CTGGTGTACGGCGCCTCTGACAGCAACGTCTATGACCTCCTAAAGGACCT
 AGAGGAAGGCATCCAAACGCTGATGGGGAGGCTGGAAGATGGCAGCCCCC
 GGACTGGCAGATCTCAAGCAGACCTACAGCAAGTTCGACACAAACTCA
 CACAACGATGACGCACTACTCAAGAACTACGGGCTGCTACTGCTTCAG
 GAAGGACATGGACAAGGTCGAGACATTCCCTGCGCATCGTGCAGTGCCGCT
 CTGTGGAGGGCAGCTGTGGCTTC (SEQ ID:16)

FIGURE 4

Growth hormone molecule 1

FPTIPLSRLFDNASLRAHRLHQIQLAFDTYQEFEAAIPKEQKYSFLQNPQT
SLCFSESIPTPSNREETQQKSNLLELRISLLLQSWLEPVQFLRSVFANS
LVYGASDSNVYDLLKDLEEGIQTLMGRLEDGSRTGQIFKQTYSKFDTNS
HNDDALLKNYGLLYCFRKDMKDVKETFLRIVQCRSVEGSCGF (SEQ ID:18)

Linker region

LVPRGSPGIGGGGG (SEQ ID:19)

Growth hormone molecule 1

FPTIPLSRLFDNASLRAHRLHQIQLAFDTYQEFEAAIPKEQKYSFLQNPQT
SLCFSESIPTPSNREETQQKSNLLELRISLLLQSWLEPVQFLRSVFANS
LVYGASDSNVYDLLKDLEEGIQTLMGRLEDGSRTGQIFKQTYSKFDTNS
HNDDALLKNYGLLYCFRKDMKDVKETFLRIVQCRSVEGSCGF (SEQ ID:18)

FIGURE 5

Leptin molecule 1

GTGCCCATCAAAAAGTCCAAGATGACACCAAAACCCCTCATCAAGACAAT
TGTACCAGGATCAATGACATTACACACACGCAGTCAGTCTCCTCCAAAC
AGAAAGTCACCGGTTGGACTTCATT CCTGGCTCCACCCC ATCCTGACC
TTATCCAAGATGGACCAGACACTGGCAGTCTACCAACAGATCCTCACCAAG
TATGCCTTCCAGAAACGTGATCAAATATCCAACAGACCTGGAGAACCTCC
GGGATCTTCTTCACGTGCTGGCCTTCTCTAAGAGCTGCCACTGCCCTGG
GCCAGTGGCCTGGAGACCTTGAGACAGCCTGGGGGTGTCCTGGAAAGCTTC
AGGCTACTCCACAGAGGTGGTGGCCCTGAGCAGGCTGCAGGGGTCTCTGC
AGGACATGCTGTGGCAGCTGGACCTCAGCCCTGGGTGC (SEQ ID:20)

Linker region

TTAGTGCCGCGCGGCAGTCCGGGCATTGGCGGCGGTGGCGGC (SEQ ID:17)

Leptin molecule 2

GTGCCCATCAAAAAGTCCAAGATGACACCAAAACCCCTCATCAAGACAAT
TGTACCAGGATCAATGACATTACACACACGCAGTCAGTCTCCTCCAAAC
AGAAAGTCACCGGTTGGACTTCATT CCTGGCTCCACCCC ATCCTGACC
TTATCCAAGATGGACCAGACACTGGCAGTCTACCAACAGATCCTCACCAAG
TATGCCTTCCAGAAACGTGATCAAATATCCAACAGACCTGGAGAACCTCC
GGGATCTTCTTCACGTGCTGGCCTTCTCTAAGAGCTGCCACTGCCCTGG
GCCAGTGGCCTGGAGACCTTGAGACAGCCTGGGGGTGTCCTGGAAAGCTTC
AGGCTACTCCACAGAGGTGGTGGCCCTGAGCAGGCTGCAGGGGTCTCTGC
AGGACATGCTGTGGCAGCTGGACCTCAGCCCTGGGTGCTAGTGCCG (SEQ ID:21)

FIGURE 6

Leptin molecule 1

VPIQKVQDDTKTLIKTIVTRINDISHTQSVSSKQKVTRGLDFIPGLHPILT
LSKMDQTLAVYQQILTSMPSRNVIQISNDLENLRDLLHVLAFSKSCHL
PWASGLETLDLGGVLEASGYSTEVVALSRLQGSLQDMLWQLDLSPGC (SEQ ID:22)

Linker region

LVPRGSPGIGGGGG (SEQ ID:19)

Leptin molecule 2

VPIQKVQDDTKTLIKTIVTRINDISHTQSVSSKQKVTRGLDFIPGLHPILT
LSKMDQTLAVYQQILTSMPSRNVIQISNDLENLRDLLHVLAFSKSCHL
PWASGLETLDLGGVLEASGYSTEVVALSRLQGSLQDMLWQLDLSPGC (SEQ ID:22)

FIGURE 7

10/502344

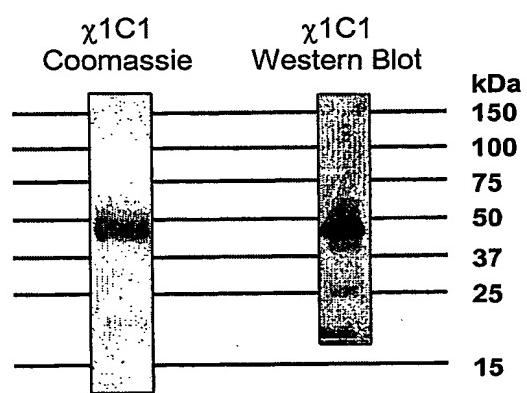


FIGURE 8

10/502344

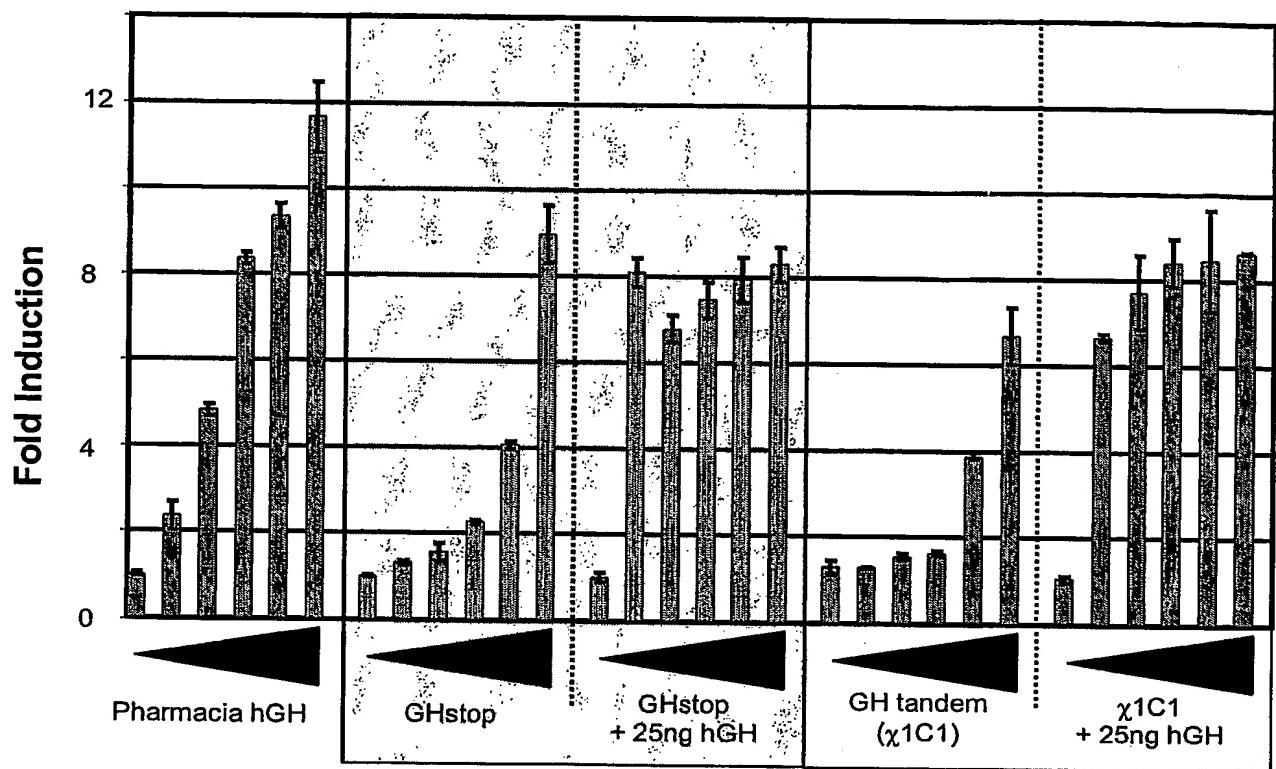


FIGURE 9

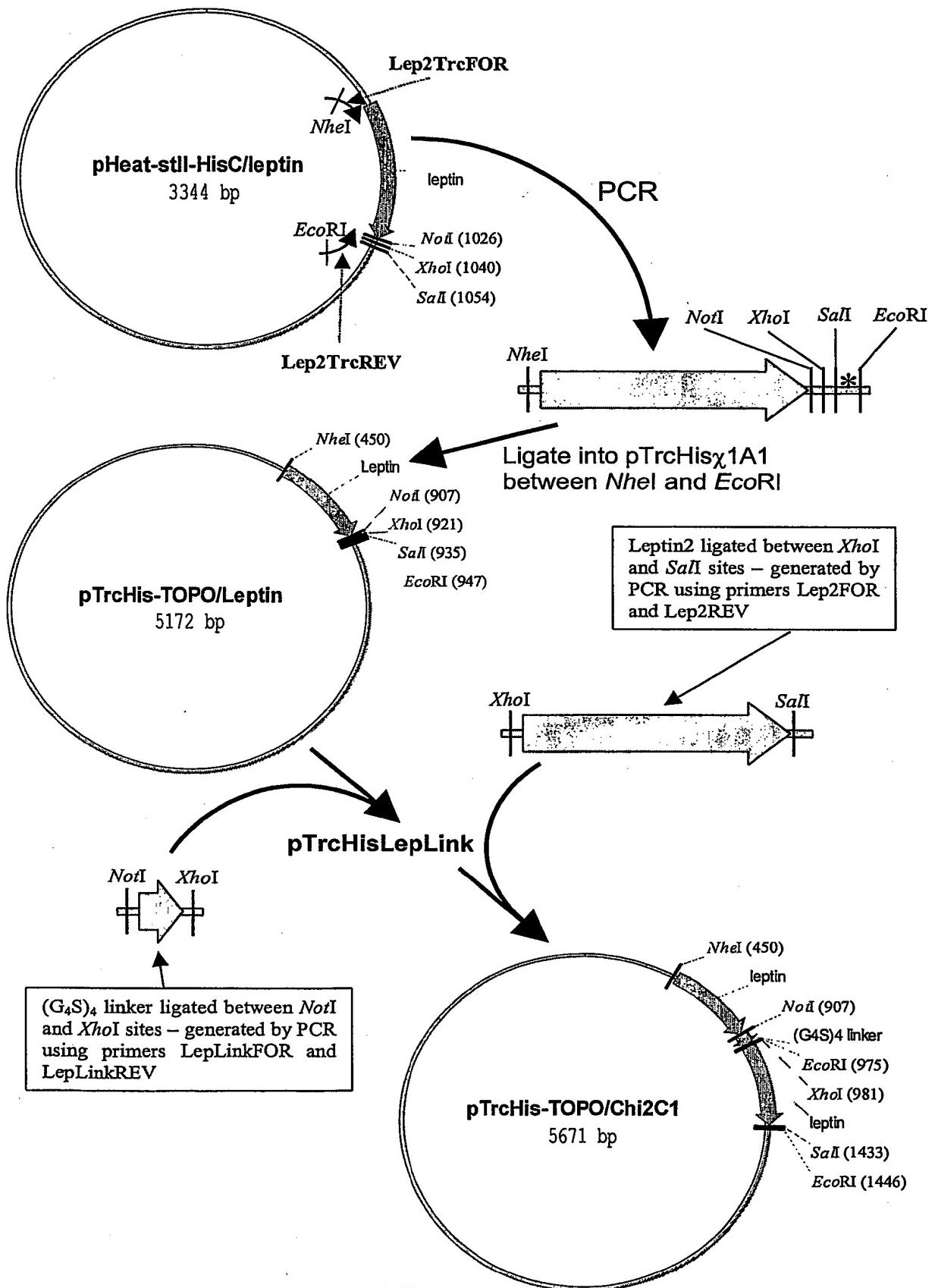


FIGURE 10

10/502344

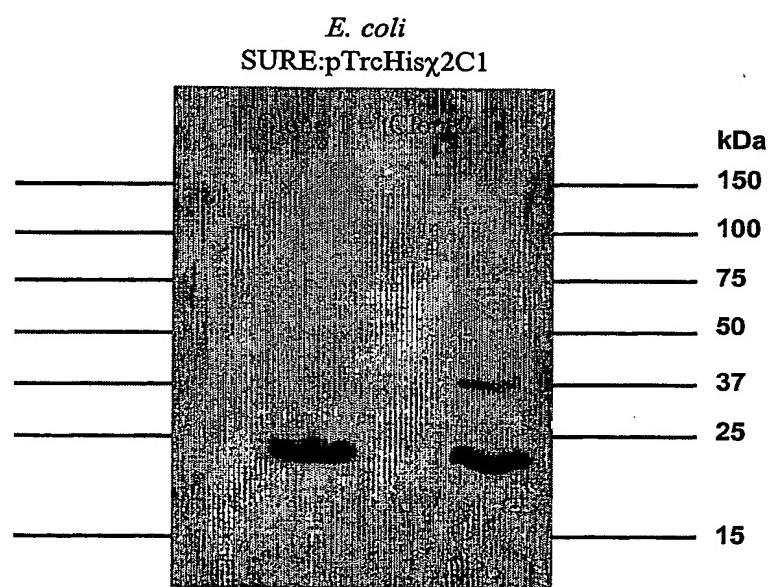


FIGURE 11

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